```
=> s paroxetine(l)(formi? or formy? or forma?)
          2997 PAROXETINE
        679681 FORMI?
         71422 FORMY?
       3069874 FORMA?
L4          105 PAROXETINE(L)(FORMI? OR FORMY? OR FORMA?)

=> s l4 and (puri? or pur?)
       1022494 PURI?
       1823011 PUR?
L5             8 L4 AND (PURI? OR PUR?)

=> d bib hit 1-8

L5   ANSWER 1 OF 8  CAPLUS  COPYRIGHT 2007 ACS on STN
AN   2006:1083758  CAPLUS
DN   146:33238
TI   An HPLC method for the indirect quantification of a quinone adduct of the
     drug paroxetine
AU   Zukowski, Janusz; Bryant, Duncan; Camilleri, Patrick
CS   Analytical Chemistry, GlaxoSmithKline, Tonbridge, Kent, UK
SO   Acta Poloniae Pharmaceutica (2006), 63(3), 175-180
     CODEN: APPHAX; ISSN: 0001-6837
PB   Polish Pharmaceutical Society
DT   Journal
LA   English
RE.CNT  5     THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB   An HPLC method was developed for the quantification of low levels of a
     catechol derivative and a quinone adduct of paroxetine in the
     presence of excess drug substance.  Due to its inherent instability, the
     paroxetine quinone adduct is not available as a pure
     compound so that an indirect method was developed for its quantification.
     This procedure is based on the assumption that one mol. of the catechol
     (or more precisely the corresponding 1,2-benzoquinone) reacts with one
     mol. of paroxetine to produce one mol. of paroxetine
     quinone adduct.  In the presence of paroxetine excess,
     pseudo-first-order kinetics was used to study the formation of
     the unstable product.  A detector response factor for the
     paroxetine quinone adduct was calculated as a function of the response
     factor for the paroxetine catechol derivative, after considering a
     mass balance of the reaction.  Using the methodol. outlined, quant. anal.
     was carried out of the paroxetine catechol derivative and the
     paroxetine quinone adduct in batches of paroxetine drug
     substance.

L5   ANSWER 2 OF 8  CAPLUS  COPYRIGHT 2007 ACS on STN
AN   2004:41440  CAPLUS
DN   140:93934
TI   Process for producing piperidine compounds, specifically
     trans-4-(4-fluorophenyl)-3-(hydroxymethyl)piperidine and derivatives,
     useful as intermediates for paroxetine
IN   Lim, Kwang-Min
PA   CLS Laboratories, Inc., S. Korea
SO   PCT Int. Appl., 15 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.          KIND   DATE        APPLICATION NO.         DATE
     --------------      ----   --------    --------------------    --------
PI   WO 2004005254        A1    20040115    WO 2003-KR1327          20030704
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
```

CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS,
LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR,
TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

| | | | | | |
|---|---|---|---|---|---|
| | KR 2004004745 | A | 20040114 | KR 2002-39088 | 20020705 |
| | AU 2003245102 | A1 | 20040123 | AU 2003-245102 | 20030704 |
| PRAI | KR 2002-39088 | A | 20020705 | | |
| | WO 2003-KR1327 | W | 20030704 | | |

OS CASREACT 140:93934; MARPAT 140:93934
RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB The invention relates to a new process for preparing pharmaceutical intermediate compds. of formula I [R1 = H, straight or branched C1-10 alkyl with or without substituent(s), straight or branched C1-10 alkoxy with or without substituent(s), aryl with or without substituent(s), formyl or alkylcarbonyl]. I are intermediates for a well-known antidepressant and selective serotonin reuptake inhibitor, paroxetine. Using the invention process, I can be prepared simply, with a high product yield and a high purity of 99% or more, without using any dangerous processes. The overall process involves (1) cyclization of an acyclic amine II [Y = leaving group, particularly Cl, Br, iodo, MeSO2O, p-MeC6H4SO2O; R1 as above; R2 = alkoxycarbonyl, arylalkoxycarbonyl, aryloxycarbonyl or cyano] and isomerization of the product, using a base, and (2) reduction of the resultant trans-isomeric piperidine compound III with a reducing agent to obtain I. For instance, treatment of II [Y = Cl, R1 = Me, R2 = CO2Me] in THF with LiN(SiMe3)2 in hexane at -10° and stirring to completion gave III [R1 = Me, R2 = CO2Me] in 95.1% yield and 98.5% purity. Reduction of the latter ester with LiAlH4 in THF at 10° gave I [R1 = Me] in 78.4% yield and 99.3% purity.

IT 109887-53-8P, trans-N-Methyl-4-(4-fluorophenyl)-3-(hydroxymethyl)piperidine 188869-26-3DP, trans-4-(4-Fluorophenyl)-3-(hydroxymethyl)piperidine, derivs. 188869-26-3P, trans-4-(4-Fluorophenyl)-3-(hydroxymethyl)piperidine 644468-14-4P, trans-N-Formyl-4-(4-fluorophenyl)-3-(hydroxymethyl)piperidine
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(target intermediate; improved preparation of trans-(fluorophenyl)(hydroxymethyl)piperidine derivs. useful as paroxetine intermediates)

L5 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2003:417743 CAPLUS
DN 139:12268
TI Preparation and compositions of N-formylparoxetine derivatives
IN Hoorn, Hans Jan; Peters, Theodorus Hendricus Antonius; Picha, Frantisek
PA Synthon B.V., Neth.
SO PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 2003044012 | A1 | 20030530 | WO 2002-NL654 | 20021015 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,

PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, US, UZ, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF,
CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

| | | | | | |
|---|---|---|---|---|---|
| CA | 2464327 | A1 | 20030530 | CA 2002-2464327 | 20021015 |
| AU | 2002330771 | A1 | 20030610 | AU 2002-330771 | 20021015 |
| EP | 1440067 | A1 | 20040728 | EP 2002-768169 | 20021015 |
| EP | 1440067 | B1 | 20041222 | | |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK | | | | |
| DE | 20220955 | U1 | 20041007 | DE 2002-20220955 | 20021015 |
| HU | 200401895 | A2 | 20041228 | HU 2004-1895 | 20021015 |
| AT | 285408 | T | 20050115 | AT 2002-768169 | 20021015 |
| NZ | 532432 | A | 20050225 | NZ 2002-532432 | 20021015 |
| PT | 1440067 | T | 20050228 | PT 2002-768169 | 20021015 |
| ES | 2230516 | T3 | 20050501 | ES 2002-2768169 | 20021015 |
| US | 2003125560 | A1 | 20030703 | US 2002-274051 | 20021021 |
| US | 6703408 | B2 | 20040309 | | |
| US | 2004147497 | A1 | 20040729 | US 2004-759437 | 20040120 |
| US | 2004266825 | A1 | 20041230 | US 2004-759436 | 20040120 |
| NO | 2004002101 | A | 20040521 | NO 2004-2101 | 20040521 |
| PRAI US | 2001-330430P | P | 20011022 | | |
| WO | 2002-NL654 | W | 20021015 | | |
| US | 2002-274051 | A3 | 20021021 | | |

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB The invention relates to a compound or composition comprising N-formylparoxetine I and 0 to 99.97% of a paroxetine selective serotonin reuptake inhibitor, comprising an effective amount of a paroxetine agent and at least one pharmaceutically acceptable excipient. The invention also relates to a process for producing a paroxetine compound which comprises treating an N-formylparoxetine compound I with a deformylation agent. A third aspect of the invention relates to a process for determining the stability or purity of a paroxetine substance or composition, which comprises assaying a paroxetine substance or composition for the presence of an N-formylparoxetine compound I, which is an impurity. For example, (3S,4R)-4-(4-fluorophenyl)piperidine-3-methanol was formylated to give N-formylparoxol (100%). Tosylation of the alc., followed by substitution with sesamol gave (3S,4R)-I, which was deformylated using MeSO3H to afford paroxetine•MeSO3H (46%).

ST formyl paroxetine prepn compn impurity

IT Stability
(of paroxetine substance or composition; preparation and compns. of N-formyl derivs. of paroxetine)

IT 5-HT reuptake inhibitors
Drug delivery systems
(preparation and compns. of N-formyl derivs. of paroxetine)

IT 533935-67-0P, N-Formylparoxetine 533935-68-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(composition impurity; preparation and compns. of N-formyl derivs. of paroxetine)

IT 7757-93-9
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(excipient; preparation and compns. of N-formyl derivs. of paroxetine)

IT 533935-65-8P, N-Formylparoxol 533935-66-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(intermediate; preparation and compns. of N-formyl derivs. of paroxetine)

IT 98-59-9, Tosyl chloride 533-31-3, Sesamol 125224-43-3, (3S,4R)-4-(4-Fluorophenyl)piperidine-3-methanol
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation and compns. of N-formyl derivs. of paroxetine)

IT 61869-08-7, Paroxetine
RL: RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(preparation and compns. of N-formyl derivs. of paroxetine)

IT 78246-49-8P, Paroxetine hydrochloride 217797-14-3P, Paroxetine methanesulfonate
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation and compns. of N-formyl derivs. of paroxetine)

IT 64006-44-6, Paroxetine maleate 72471-80-8, Paroxetine acetate
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation and compns. of N-formyl derivs. of paroxetine)

L5 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2002:977660 CAPLUS
DN 138:29184
TI A process for preparing paroxetine hydrochloride limiting formation of pink compounds
IN Avrutov, Ilya; Pilarski, Gideon
PA Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals USA, Inc.
SO PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 2002102382 | A1 | 20021227 | WO 2002-US19016 | 20020614 |
| | WO 2002102382 | A9 | 20030306 | | |
| | W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW | | | | |
| | RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| | CA 2447808 | A1 | 20021227 | CA 2002-2447808 | 20020614 |
| | US 2003083501 | A1 | 20030501 | US 2002-172521 | 20020614 |
| | EP 1406625 | A1 | 20040414 | EP 2002-752054 | 20020614 |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| | CN 1516585 | A | 20040728 | CN 2002-811890 | 20020614 |
| | HU 200400216 | A2 | 20040728 | HU 2004-216 | 20020614 |
| | TR 200302081 | T2 | 20040921 | TR 2003-2081 | 20020614 |
| | JP 2005501819 | T | 20050120 | JP 2003-504969 | 20020614 |
| | ZA 2003009049 | A | 20041121 | ZA 2003-9049 | 20031120 |
| PRAI | US 2001-298603P | P | 20010614 | | |
| | US 2001-326993P | P | 20011005 | | |
| | US 2002-346048P | P | 20020104 | | |
| | WO 2002-US19016 | W | 20020614 | | |

RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI A process for preparing paroxetine hydrochloride limiting formation of pink compounds

ST paroxetine hydrochloride purity prepn; buffer paroxetine hydrochloride purity prepn

IT Mental and behavioral disorders
(depression; preparation of paroxetine hydrochloride limiting formation of pink compds.)

IT Mental and behavioral disorders
(obsession-compulsion; preparation of paroxetine hydrochloride limiting formation of pink compds.)

IT Anxiety
(panic disorder; preparation of paroxetine hydrochloride limiting formation of pink compds.)

IT Mental and behavioral disorders
(post-traumatic stress disorder; preparation of paroxetine hydrochloride limiting formation of pink compds.)

IT Ovarian cycle
(premenstrual syndrome; preparation of paroxetine hydrochloride limiting formation of pink compds.)

IT Antioxidants
Anxiety
Buffers
Parkinson's disease
Recrystallization
(preparation of paroxetine hydrochloride limiting formation of pink compds.)

IT 7440-44-0, Carbon, uses
RL: MOA (Modifier or additive use); USES (Uses)
(activated; preparation of paroxetine hydrochloride limiting formation of pink compds.)

IT 50-81-7, Ascorbic acid, uses 128-37-0, BHT, uses 25013-16-5, BHA
RL: MOA (Modifier or additive use); USES (Uses)
(antioxidant; preparation of paroxetine hydrochloride limiting formation of pink compds.)

IT 12125-02-9, Ammonium chloride, uses
RL: MOA (Modifier or additive use); USES (Uses)
(preparation of paroxetine hydrochloride limiting formation of pink compds.)

IT 67-56-1, Methanol, uses 67-64-1, Acetone, uses
RL: NUU (Other use, unclassified); PEP (Physical, engineering or chemical process); PYP (Physical process); PROC (Process); USES (Uses)
(preparation of paroxetine hydrochloride limiting formation of pink compds.)

IT 61869-08-7, Paroxetine
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of paroxetine hydrochloride limiting formation of pink compds.)

IT 78246-49-8P, Paroxetine hydrochloride 110429-35-1P, Paroxetine hydrochloride hemihydrate
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of paroxetine hydrochloride limiting formation of pink compds.)

L5 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2002:832615 CAPLUS
DN 137:329533
TI Optimized procedures for the manufacture of paroxetine salts
IN Upadhyaya, Subhash P.; Ronsen, Bruce
PA Pentech Pharmaceuticals, Inc., USA
SO PCT Int. Appl., 55 pp.
CODEN: PIXXD2

DT Patent
LA English
FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI WO 2002085360 | A1 | 20021031 | WO 2002-US13378 | 20020425 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2003032809 | A1 | 20030213 | US 2002-133726 | 20020425 |
| PRAI US 2001-286590P | P | 20010425 | | |
| US 2001-290411P | P | 20010511 | | |
| US 2001-295471P | P | 20010601 | | |
| US 2001-333530P | P | 20011120 | | |

RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Methods for manufacturing amorphous paroxetine hydrochloride by mixing a carboxylic acid salt of paroxetine with hydrogen chloride and isolating the amorphous paroxetine hydrochloride are described. Also described herein are methods for manufacturing substantially pure paroxetine free base and methods for obtaining paroxetine salts with carboxylic acids, such as paroxetine acetate, paroxetine trifluoroacetate, and paroxetine formate, or with mineral acids, such as paroxetine carbonate, paroxetine phosphate, paroxetine sulfate, and analogous salts thereof. The paroxetine salts may be formulated for the use in treatment of medical disorders.

IT 72471-80-8P, Paroxetine acetate 236391-41-6P, Paroxetine propionate 236391-42-7P, Paroxetine formate 473829-66-2P 473829-67-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(optimized procedures for manufacture of paroxetine salts for dosage forms)

L5 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2000:911247 CAPLUS
DN 134:61560
TI Process for the production of paroxetine hydrochloride
IN Jones, David Alan
PA Smithkline Beecham P.L.C., UK
SO PCT Int. Appl., 14 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI WO 2000078752 | A1 | 20001228 | WO 2000-GB2425 | 20000622 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, | | | | |

CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRAI GB 1999-14585 A 19990622
RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB Paroxetine-HCl is prepared by a process in which a suspension of paroxetine maleate is treated with an excess of HCl to form a solution containing paroxetine, maleic acid, and HCl, and crystallizing substantially pure paroxetine-HCl from the solution In this process paroxetine maleate in solution is directly converted to solid paroxetine hydrochloride, avoiding formation of paroxetine free base and subsequent re-acidifying with hydrogen chloride. The process surprisingly results in good yield and purity without the complication of large amts. of maleic acid contamination, and so is suitable for large-scale manufacture
IT 110-16-7, Maleic acid, formation (nonpreparative)
RL: FMU (Formation, unclassified); FORM (Formation, nonpreparative)
(process for the production of paroxetine hydrochloride)

L5 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1999:227255 CAPLUS
DN 131:67604
TI O- and N-demethylation of venlafaxine in vitro by human liver microsomes and by microsomes from cDNA-transfected cells: effect of metabolic inhibitors and SSRI antidepressants
AU Fogelman, Steven M.; Schmider, Jurgen; Venkatakrishnan, Karthik; Von Moltke, Lisa L.; Harmatz, Jerold S.; Shader, Richard I.; Greenblatt, David J.
CS Department of Pharmacology and Experimental Therapeutics, Tufts University School of Medicine, Boston, MA, 02111, USA
SO Neuropsychopharmacology (1999), 20(5), 480-490
CODEN: NEROEW; ISSN: 0893-133X
PB Elsevier Science Inc.
DT Journal
LA English
RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB The biotransformation of venlafaxine (VF) into its two major metabolites, O-desmethylvenlafaxine (ODV) and N-desmethylvenlafaxine (NDV) was studied in vitro with human liver microsomes and with microsomes containing individual human cytochromes from cDNA-transfected human lymphoblastoid cells. VF was coincubated with selective cytochrome P 450 (CYP) inhibitors and several selective serotonin reuptake inhibitors (SSRIs) to assess their inhibitory effect on VF metabolism Formation rates for ODV incubated with human microsomes were consistent with Michaelis-Menten kinetics for a single-enzyme mediated reaction with substrate inhibition. Mean parameters determined by non-linear regression were: Vmax = 0.36 nmol/min/mg protein, Km = 41 μM, and Ks 22901 μM (Ks represents a constant which reflects the degree of substrate inhibition). Quinidine (QUI) was a potent inhibitor of ODV formation with a Ki of 0.04 μM, and paroxetine (PX) was the most potent SSRI at inhibiting ODV formation with a mean Ki value of 0.17 μM. Studies using expressed cytochromes showed that ODV was formed by CYP2C9, -2C19, and -2D6. CYP2D6 was dominant with the lowest Km, 23.2 μM, and highest intrinsic clearance (Vmax/Km ratio). No unique model was applicable to the formation of NDV for all four livers tested. Parameters determined by applying a single-enzyme model were Vmax = 2.14 nmol/min/mg protein, and Km = 2504 μM. Ketoconazole was a potent inhibitor of NDV production, although its inhibitory activity was not as great as observed with pure 3A substrates. NDV formation was also reduced by 42% by a polyclonal rabbit antibody against rat liver CYP3A1. Studies using expressed cytochromes showed that NDV was formed by CYP2C9, -2C19, and -3A4. The highest intrinsic clearance was attributable to CYP2C19 and the lowest to CYP3A4. However the high in vivo abundance of 3A isoforms will magnify the importance of this cytochrome.

Fluvoxamine (FX), at a concentration of 20 μM, decreased NDV production by 46% consistent with the capacity of FX to inhibit CYP3A, 2C9, and 2C19. These results are consistent with previous studies that show CYP2D6 and -3A4 play important roles in the formation of ODV and NDV, resp. In addition the authors have shown that several other CYPs have important roles in the biotransformation of VF.

L5 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1992:17824 CAPLUS
DN 116:17824
TI Radiosynthesis and evaluation of N-(3-[18F]fluoropropyl)paroxetine as a radiotracer for in vivo labeling of serotonin uptake sites by PET
AU Suehiro, Makiko; Wilson, Alan A.; Scheffel, Ursula; Dannals, Robert F.; Ravert, Hayden T.; Wagner, Henry N., Jr.
CS Div. Nucl. Med., Johns Hopkins Med. Inst., Baltimore, MD, 21205-2179, USA
SO Nuclear Medicine and Biology (1991), 18(7), 791-6
CODEN: NMBIEO; ISSN: 0883-2897
DT Journal
LA English
AB To visualize serotonin uptake sites by positron emission tomog. (PET), N-(3-[18F]fluoropropyl)paroxetine ([18F]FPP) (I), a derivative of the selective serotonin uptake blocker paroxetine, was synthesized from 3-[18F]fluoropropyltosylate and paroxetine via a 1-pot procedure. The rate of formation of [18F]FPP was a function of the ratio of the initial amount of paroxetine to that of 1,3-propanediol bistosylate with which [18F]fluoropropyltosylate was synthesized. When the reaction mixture contained an excess amount of paroxetine over that of the propyl-bistosylate, the radiosynthesis followed by HPLC purifn., which took .apprx.90 min, gave [18F]FPP in a radiochem. yield of .apprx.8%, and in high radiochem. and chemical purity. The specific activity was 2640 ± 360 mCi/μmol. The brain biodistribution of [18F]FPP showed no distinguishable localization in regions with high d. of serotonin uptake sites such as hypothalamus or olfactory tubercles. In vitro binding assays revealed that N-fluoropropylation of paroxetine reduced the affinity for the serotonin uptake site by 3 orders of magnitude.